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Review Article

An Overview of Transdermal Drug Delivery System (TDDS)

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ABSTRACT

Oral medications often fall short of desired efficacy. To address this limitation, transdermal drug delivery systems (TDDS) have emerged as a viable alternative. TDDS involve delivering drugs through the skin to achieve systemic effects, differing from traditional topical applications. These systems transport drugs to viable skin tissues, producing local therapeutic effects while also releasing a significant fraction into systemic circulation. The adhesive used in TDDS plays a crucial role in ensuring product safety, efficacy, and quality. Transdermal delivery offers several advantages over traditional oral and invasive methods, including reduced hepatic first-pass metabolism, enhanced therapeutic efficiency, and steady plasma drug levels. TDDS provide a promising approach to improve treatment outcomes, and their development continues to advance with innovative technologies and materials. This approach has the potential to revolutionize the way medications are delivered. In enhancing therapeutics outcomes for various diseases including pain management, hypertension, diabetes and neurological disorders. This abstract provides an overview of their potential of revolutionize the field of pharmacotherapy.

INTRODUCTION

A drug delivery system (DDS) utilizes various technologies to control the release of active substances into the body, maximizing therapeutic effects while minimizing side effects. [1,2] DDS encompasses various routes of administration, including mucosal, oral, transdermal, inhalation, and intravenous injection. Transdermal drug delivery systems (TDDS) are a widely investigated non-invasive method for delivering therapeutic agents through the skin, bypassing conventional injection methods.[3,5] TDDS has significantly impacted pain management, hormonal treatments, and diseases affecting the cardiovascular and central nervous systems. By avoiding the gastrointestinal tract, TDDS eliminates first-pass metabolism and interference from pH, enzymes, and intestinal bacteria. This approach enables controlled drug release, contributing to high patient compliance. [6,9]The non-invasive nature of

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TDDS minimizes pain and burden on patients, making it an attractive option for pediatric and geriatric populations. However, the innate skin barrier limits the full potential of TDDS. The skin's multi-layered structure, comprising the epidermis and dermis, protects the body from environmental hazards but also interferes with transdermal delivery.[10]The stratum corneum, the outermost layer of the epidermis, poses a significant barrier to substance transport, particularly for large molecular weights. In contrast, substances with small molecular weights utilize the intracellular pathway in TDDS. [11]

DISCUSSION

Advantages of transdermal drug delivery : [12]

1. Avoiding first-pass metabolism, reducing side effects, and minimizing fluctuations in plasma levels.
2. Utilizing drug candidates with short half-lives and low therapeutic indices.
3. Easy elimination of drug delivery in case of toxicity.
4. Reduced dosing frequency, enhancing patient compliance.

Limitation transdermal drug delivery systems *:* [12]

1. Difficulty in penetrating the stratum corneum with large drug molecules.
2. Inability of drugs with low or high partition coefficients to reach the bloodstream.
3. Limited skin permeability.
4. Significant lag time.
5. Potential skin irritation and allergic responses.

The first transdermal therapeutic patch was introduced by Alza Corporation in 1980 for motion sickness treatment. Since then, many companies have developed commercial transdermal delivery products. Currently, TDDS preparations are available as matrix systems, reservoir systems, and systems with or without rate-controlling membranes. Various medications, including Alprazolam, Atenolol, and Insulin, are being explored for transdermal administration. [13,14]

ANATOMY AND PHYSIOLOGY OF SKIN

The human skin, covering an area of 1.5-2.0 m^2 in adults, is the largest organ in the body by mass. The transdermal route has been utilized to treat various diseases and conditions, offering a promising alternative to traditional drug delivery systems. [15]The use of transdermal delivery systems gained momentum in the late 20th century. This novel route offers several advantages over conventional systems, including reduced systemic toxicity, increased skin permeability, improved bioavailability of gastrointestinally degraded drugs, and overcoming first-pass metabolism. The ultimate goal of transdermal drug design is to optimize these benefits, providing enhanced therapeutic outcomes. [16, 17]

Epidermis[18,19] *:*

The epidermis, the outermost skin layer, has a thickness ranging from 0.06 mm on the eyelids to 0.8 mm on the palms and soles. It consists of multiple layers, primarily covered by the Stratum Corneum (SC) and the viable epidermis.

Stratum Corneum:[20-22]

The stratum corneum (SC), also known as the horny layer, is the outermost skin layer. It's composed of 10-25 layers of dead, keratinized cells called corneocytes.. The protein component is primarily made up of alpha-keratin, while the lipid fraction is structured in bilayers, containing amphiphilic materials like cholesterol and fatty acids.

Viable epidermis: [23]

Beneath the stratum corneum (SC), the viable epidermis varies in thickness from 0.06 mm on the eyelids to 0.8 mm on the palms. It consists of multiple inward layers, including the stratum basal, stratum lucidum, stratum granulosum, and stratum spinosum.

Table 1 : Layers of epidermis [22]

Layers of Epidermis	Latin name
Basal cell layer	Stratum Basale
Prickle	Stratum Spinosum
Granular layer	Stratum Granulosum
Clear layer	Stratum Lucidum
Horny layer	Stratum Corneum

Dermis:

The dermis, a 3-5 mm thick layer of connective tissue, houses blood, lymph, and nerve vessels. It plays a vital role in regulating body temperature, supplying the skin with nutrients and oxygen, and removing waste. Additionally, the cutaneous blood supply facilitates transdermal permeation by maintaining a low dermal concentration, creating a concentration gradient that enables molecules to penetrate the skin barrier. [24]

Hypodermis:

The dermis and epidermis are anchored by the hypodermis, a layer of subcutaneous fat tissue that stores energy, provides mechanical protection, regulates temperature, and facilitates nutrient supply.. In contrast, topical drug administration requires the medication to penetrate only the stratum corneum (SC) before being retained in the skin layers. [25]

FUNCTIONS OF THE SKIN [26 , 27]

The skin performs several vital functions, including:

1. Protection: shielding the body from dehydration, minor injuries, chemicals bacteria, and UV radiation.
2. Sensation: responding to stimuli through sensory nerve action.
3. Thermoregulation: maintaining a stable body temperature (around 36.8°C or 98.4°F) despite external temperature fluctuations.
4. Vitamin D production: converting 7-dehydrocholesterol into vitamin D upon exposure to sunlight.
5. Barrier function: preventing the absorption of harmful substances, such as mercury and certain low-molecular-weight drugs.

ROUTES OF SKIN PERMEATION

During percutaneous permeation, a drug molecule can penetrate the epidermis directly or diffuse through shunts, such as hair follicles and eccrine glands. Initially, drug molecules may enter the skin through hair follicles or sweat ducts and then be absorbed by the follicular epithelium and sebaceous glands. There are three possible pathways for pharmaceutical particles to penetrate the skin: through sweat glands, hair follicles, and sebaceous organs (collectively known as the shunt or appendageal channel), or directly across the stratum corneum. [28 , 29]

I. **. Appendageal route:**

The appendageal pathway involves the passage of substances through hair follicles, sweat glands, and associated sebaceous glands. Since these channels bypass the stratum corneum (SC), they are referred to as "shunt" pathways. [30]

II. **. Epidermal route:**

Two potential routes for pharmaceuticals to penetrate the skin are the transcellular (intracellular) and intercellular pathways. These routes allow smaller molecules to pass through the stratum corneum (horny layer) with relative ease. [31 , 32]

BASIC COMPONENTS OF TDDS

1. Polymer :

Polymers play a crucial role in Transdermal Drug Delivery Systems (TDDS), regulating the release of the drug from the device. A polymer matrix is

created by dispersing the drug in a liquid or solid synthetic polymer base. Ideally, these polymers should ensure consistent and effective drug delivery throughout the product's shelf life, while also being safe for use. Polymers form the foundation of transdermal medication delivery systems. [33]

Table 2 : Different types of polymer

Polymer	Examples
Natural polymer	Starch, Cellulose, Gelatin, Proteins, Gums, and their derivatives
Synthetic polymer	Polyvinylpyrrolidone, Polypropylene, Polyamide, Polyvinyl alcohol, Polyethylene, Polyvinyl chloride, Polyurea
Synthetic elastomers	Polysiloxane, Polybutadiene, Butyl rubber, Silicone rubber.

2. Active pharmaceutical ingredient (API) :

Criteria for selecting drug for transdermal drug delivery:

- **Physicochemical properties:**
- Molecular weight: Less than 500 Daltons.
- Solubility and affinity: Balanced in both hydrophilic and lipophilic layers, with an optimal partition coefficient.
- Melting point: Low melting point, which enhances the drug molecule's ability to penetrate the skin.
- **Biological properties:**
- Daily dosage: A relatively small daily dose of a few milligrams is ideal.
- Half-life: A shorter half-life (t 1/2) facilitates transdermal distribution.
- Skin tolerance: Drugs that cause irritation, allergic reactions, or tolerance development are not suitable.
- Metabolism: Drugs that undergo gastrointestinal inactivation or hepatic first-pass metabolism are good candidates for transdermal delivery systems (TDDS). [33]

3. Adhesive:

Adhesives play a crucial role in transdermal drug delivery systems (TDDS) by:Securing the patch to the skin. Holding the patch components together. To ensure the patch stays in place, the adhesive must have strong adhesion properties. Commonly used adhesives include: Pressure-sensitive adhesives, Polyacrylate-based adhesives, Silicone-based adhesives, Poly-isobutylene-based adhesives

Adhesives for TDDS must meet the following requirements:

- Be easily absorbed into the skin
- Be easy to remove
- Not cause skin irritation
- Be compatible with the medication, permeation enhancers (PEs), and device excipients. [34]

4. **Solvents**

- Water, alcohols (methanol and ethanol)
- Miscellaneous Solvents -(propylene-glycol, glycerol, isopropyl-palmitate)
- Pyrrolidones – 2 pyrrolidone, N-methyl, 2-purrolidone; laurocapram (Azone)
- Alkyl Methyl Sulfoxides-dimethyl sulfoxide, alkyl homologues of methyl sulfoxide , dimethyl acetamide and dimethyl formamide[35].

5. **Membrane**

The rate-controlling membrane in transdermal patches regulates the release of the drug from the reservoir or multilayer patches. Key characteristics of this membrane include:

Regulated drug release: Controls the rate at which the drug is released.

Flexibility: Should be flexible enough to withstand bending or stretching without splitting or cracking.Material options: Common materials used for rate-controlling membranes include:

a. Polyethylene sheets

b. Cellulose acetate
c. Ethylene vinyl acetate co-polymer[36].

6. **Plasticizers**

Selecting the right plasticizer at the optimal concentration significantly affects the mechanical properties and drug permeability of transdermal patches. Commonly used plasticizers include:
Glycerol
Propylene glycol
Dibutyl phthalate (DBP)
Fatty acid esters
Phthalate esters
Polyethylene glycol 200 (PEG 200) [36].

7. Permeation Enhancers (PEs)

Compounds incorporated into transdermal patches to alter solubility, diffusivity, and barrier properties of the stratum corneum (SC), enhancing drug permeation.

Solvents : Methanol, ethanol, dimethyl sulfoxide, dimethyl acetamide, 2- pyrrolidone,propylene glycol, glycerol etc.

Surfactants: Sodium lauryl sulphate, Decodecylmethylsulphoxide

Fatty acids: Oleic acid, undecanoic acid Fatty alcohols Octanol

Terpenes: Menthol, thymol, d-limonene, 1-8 cineole

Sulfoxides : Dimethyl sulfoxide ,Sugars Cyclodextrins ,Lactam Laurocapram (azone) [36]

FORMULATION APPROACHES USED IN DEVELOPMENT OF TDDS

1. Polymer Membrane Permeation Controlled TDDS:

In Membrane Permeation Controlled Systems, the drug reservoir is sandwiched between a rate-controlling membrane and an impermeable backing layer. The drug is either dissolved in a solvent or suspended in a polymer matrix, and the rate-controlling membrane regulates its release. Examples of FDA-approved systems include Transderm-Nitro, Transderm-SCOP, and Catapres-TTS[37]

2. Polymer Matrix Diffusion Controlled TDDS:

Distributing the solid drug uniformly in a hydrophilic or lipophilic polymer matrix.
Molding the matrix into medicated disks with predetermined thickness and surface area. Placing the disk in a compartment with a plastic backing and occlusive base plate.
Creating an adhesive border strip around the edge of the patch.
Examples include the Nitro-Dur, Minitran, and Nitro-Dur II systems. The advantage of this system is that it prevents dose dumping, as the polymer cannot rupture.[37].

3. Microreservoir dissolution controlled TDDS:

Matrix Diffusion-Controlled Systems: A transdermal drug delivery system where the drug reservoir is formed by suspending drug solids in a water-soluble liquid polymer, then dispersing it in a lipophilic polymer. The system can be modified with an additional biocompatible polymer layer to control the drug release rate.
Example: Nitroglycerin TDDS for angina pectoris. [38]

4. Drug reservoir gradient controlled TDDS

Gradient-Reservoir Matrix System: A modified polymer matrix system where the drug loading level increases incrementally, forming a gradient of drug reservoir across multiple laminate adhesive layers. This design overcomes non-zero order drug release profiles.
Examples - Nitroglycerine-containing Deponit TDDS for angina pectoris[38]

KINETICS OF TRANSDERMAL PERMEATION [39 ,40]

For transdermal penetration to occur, a medicine must have specific physicochemical properties. The rate of skin penetration is influenced by several factors, including:

dQ/dt = Ps (Cd-Cr) …….... (1)

The skin's permeability coefficient (Ps) is determined by the following relationship:

Ps = (Cd - Cr) / (skin thickness)

Where:Cd = donor compartment concentration

Cr = receptor compartment concentration

Ps =Ks.Dss/Hs…… (2)

The penetrability coefficient (Ps) of a skin penetrant remains constant if three conditions are met:

1. Ks (partition coefficient) remains constant.
2. Dss (apparent diffusivity) remains constant.
3. Hs (total skin thickness) remains constant.

dQ/dt= Ps.Cd…… (3)

During skin saturation, the rate of skin penetration (dQ/dt) remains constant because the size of the donor compartment (Cd) stays relatively stable. To maintain a constant Cd, the drug delivery rate (Rr) must be faster than or equal to the skin absorption rate (Ra). This ensures that Cd remains at or above the drug's solubility in the stratum corneum (Cs), resulting in a high rate of skin saturation.

(dQ/dt)m =Ps.Cs…… (4)

The skin penetrability coefficient (Ps) and the solubility of the drug in the stratum corneum (Cs) determine the maximum rate of skin penetration. This suggests that the stratum corneum is the limiting factor in skin penetration. Studies using rhesus monkeys and in-vitro tests with freshly removed skin have been conducted to investigate this hypothesis.

METHODS FOR PREPARATION OF TDDS[41]

The following methods for preparation of TDDS are:

1. **Asymmetric TPX membrane preparation method**

To create patches, a backing membrane made of heat-sealable polyester film with a 1 cm diameter concave is used. The process involves:

1. Injecting the drug sample into the concave membrane.
2. Sealing the membrane with an adhesive.
3. Coating with an asymmetric TPX (poly(4-methyl-1-pentene)) membrane.

2. **Circular Teflon mould method**

Preparation of Polymer Films begins with dissolving polymers in different ratios using an organic solvent. The calculated amount of medication is then dissolved in half the amount of the same organic solvent. Enhancers are dissolved in varying concentrations in the remaining organic solvent and added to the drug-polymer solution. DBP is added as a plasticizer and the mixture is stirred for 12 hours. The mixture is then poured into a round Teflon mold. To regulate solvent vaporization, the mold is placed on a flat surface and covered with an inverted funnel in a laminar flow hood with an air speed of 0.5 m/s. The solvent is left to evaporate for 24 hours. Finally, the formed films are evaluated within a week of preparation.

3. **Mercury substrate method**

This method involves dissolving the drug in a polymer solution with a plasticizer. The solution is then stirred for 10-15 minutes to create a uniform mixture. Next, the mixture is poured onto a levelled mercury surface and covered with an inverted funnel to control the rate of solvent evaporation.

4. **Solvent Casting Method**

The solvent casting method involves mixing the drug and excipients with a solvent using a magnetic stirrer to create a uniform solution. The solution is then poured into a petri-plate and dried in a hot air oven or under vacuum to form a solid film.

5. **“IPM membranes” method**

To prepare the gel, the required medication is dissolved in a solution of water, propylene glycol, and carbomer 940 polymer using a magnetic stirrer. The mixture is stirred for 12 hours. Triethanolamine is added to neutralize the dispersion and increase its viscosity. For poorly soluble medications, a buffer solution of pH 7.4

can be used to create the gel. The resulting gel is then incorporated into an Isopropyl myristate (IPM) membrane.

6. Ethylene Vinylacetate copolymer (EVAC) membranes method

To create a transdermal therapeutic system, rate-control membranes such as polyethylene, ethylene vinyl acetate copolymer (EVAC), and 1% Carbopol reservoir gel can be used. The gel is prepared by dissolving the drug in propylene glycol (if water-insoluble) and then adding Carbopol resin, which is neutralized with a 5% sodium hydroxide solution. The gel is applied to a backing layer sheet, and a rate-regulating membrane is placed on top. The edges are heat-sealed to create a leak-proof device.

7. Aluminium backed adhesive film method

When the loading dose for a transdermal drug delivery system exceeds 10 mg, unstable matrices can occur. In such cases, the sticky film approach with an aluminum backing is suitable. Chloroform is the preferred solvent for preparing the solution, as most drugs and adhesives are soluble in it. The preparation process involves:

1. Dissolving the medication in chloroform.
2. Adding adhesive substance to the drug solution and dissolving it.
3. Lining a specially constructed aluminum former with aluminum foil.
4. Securing cork blocks at the ends to create a uniform film.

8. Pro-liposomes:

Film deposition technique is used to create liposomes in the carrier approach. An ideal ratio of 0.1:2.0 between the drug and lecithin can be employed. Here's the step-by-step process:

Add 5 mg of mannitol powder to a 100 ml round-bottom flask at 60-70°C.Swirl the flask at 80-90 rpm and vacuum-dry for 30 minutes. Cool the water bath to 20-30°C. Dissolve the drug and lecithin in an organic solvent mixture.Add 0.5 ml of the solution to the flask at 37°C and dry completely. Attach the flask to a lyophilizer after the final loading. Store the resulting pro-liposome powder in a desiccator overnight. Sieve the powder through 100 mesh and store it in a glass bottle at freezing temperature until characterization.

FACTORS AFFECTING TRANSDERMAL PATCHES[41]

There are various factors which affects the action of transdermal patches.

***A]* Physicochemical Properties**

i. Partition coefficient
ii. Molecular size
iii. Solubility/melting point
iv. Ionization

***B]* Physiological & Pathological Conditions of Skin**

i. Reservoir effect of horny layer
ii. Lipid film
iii. Skin hydration
iv. Skin temperature
v. Regional variation
vi. Pathological injuries to the skin
vii. Cutaneous self-metabolism
viii. Skin barrier properties in the neonate and young infant
ix. Skin barrier properties in aged skin
x. Race
xi. Body site
xii. Penetration enhancers

EVALUATION OF TRANSDERMAL PATCHES [42]

1.Physical appearance

These includes visual inspection for characteristics such as color, clarity, flexibility and surface smoothness.

2. Patch thickness

The thickness of the drug-loaded patch was measured at multiple points using a digital micrometer, and the average thickness and standard deviation were calculated to ensure uniformity of the prepared patch.

3.Weight variation

Patches were dried at 60°C for 4 hours. Samples were cut, weighed, and average weight and standard deviation calculated.

4. Folding endurance

A strip of standardized area was cut and repeatedly folded at the same point until it broke. The folding endurance was determined by the number of folds achieved without rupture.

5. Surface pH of the transdermal patches

Measures patch surface pH using pH meter to ensure it's within skin-friendly range (4.5-6.5).

6. Swelling index

The swelling index was determined using the diameter method. Agar solution (pH 7.4) was prepared and poured into a petri dish. The initial diameter of each patch was measured, then allowed to swell on the agar gel surface. Diameter measurements were taken at 2, 5, and 7 hours, with results recorded as the mean of three readings. The 7-hour study duration was chosen based on the recommended residence time.

Swelling index = Wt –Wo / Wo

7. Drug content

A prepared transdermal patch was dissolved in 100ml of PBS (pH 7.4) using a magnetic stirrer (12h) and sonication (30min). After filtering out insoluble residue, the filtrate was diluted and its absorbance measured using a UV spectrophotometer.

8. Flatness study

A flatness study was conducted to evaluate the surface smoothness and dimensional stability of the prepared transdermal patches. Three strips were cut from different areas of the film and their lengths measured. The percent constriction was calculated to determine the flatness, with 0% constriction indicating 100% flatness.

$(l\,1 - l\,2)/l\,1 \times 100$

9. Measurement of tensile strength (TS) and Percentage elongation (E/B)

The mechanical properties of the patches were evaluated using a tensile strength apparatus. Patch strips with precise dimensions and no imperfections were clamped 3 cm apart. The top clamp pulled the strips at a rate of 100 mm/min, measuring force and elongation until breakage. Results were discarded if the patch broke between the clamps. Three measurements were taken for each patch. Two key properties were calculated: Tensile Strength (TS), the maximum stress at breakage, and Elongation at Break (% E/B).

Tensile Strength = Force At Break / Intial Cross Section Area Of The Sample (mm2)

% Elongation = (Increase In Length / Original Length) X 100

10. Percent moisture absorption

Transdermal patches were precisely weighed and stored in desiccators with 100ml of aluminum chloride solution, maintaining humidity levels of 76% and 86%. After 3 days, the patches were removed and reweighed.

Percent Moisture Absorption =

(Final Weight of the Patch−Initial Weight of the Patch / Initial Weight of the Patch) X100

11. Percent moisture loss

The transdermal patches were precisely weighed and stored in desiccators with anhydrous calcium chloride for 3 days. After removal and reweighing, the percentage of moisture absorbed and lost was calculated.

percent Moisture loss =

(Intial Weight of the Patch – final weight of the Patch / intial weight of the Patch) X 100

12. In-vitro release study

A drug release study was conducted using a USP Type-1 basket dissolution test apparatus. Patches were immersed in 250ml of PBS solution (pH 7.4) at 37°C, stirred at 50rpm. 5ml samples were withdrawn every 30 minutes, filtered, diluted, and analyzed spectrophotometrically. The experiment was run in triplicate, and average values were reported.

13. Ex- vivo permeation study

An Ex- vivo permeation study was conducted using a modified Franz diffusion cell. Phosphate buffer solution (pH 7.4) was used as the diffusion medium. Samples were withdrawn from the receptor compartment at set intervals and analyzed using a UV-Visible spectrophotometer.

14. Stability study

Stability testing of drug products follows FDA and ICH guidelines. Long-term testing is typically done at 25°C/60% RH for 6 months. If significant changes occur, intermediate testing at 30°C/75% RH is recommended.

15. Kinetic modelling of dissolution data

Predicting a formulation's bioperformance using in vitro dissolution data is crucial for developing controlled-release formulations. To determine the best drug release mechanism, in vitro release data was fitted into models like zero-order, first-order, Higuchi, and Korsmeyer-Peppas. The model with the highest correlation coefficient was selected to describe the release mechanism.

$Qt = Q0 + K0t$: Zero order model (i)

$\log C = \log CKt/2.303$: First order model (ii)

$ft = Q = KH \times t1/2$: Higuchi model (iii)

$Mt/M\infty = Ktn$: Korsmeyer–Peppas model (iv)

CONCLUSION

Transdermal drug delivery systems offer a promising approach for delivering medications through the skin , providing a convenient, pain-free and controlled release of therapeutic agents. TDDS have been shown to improve patient compliance, reduce side effects, and enhance bioavailability. With advancements of technology and materials science, TDDS have become increasingly sophisticated, allowing for tailored release profiles and targeted delivery. The evaluation of TDDS involves a range of physical, chemical and biological tests to ensure their safety, efficacy, and quality. Overall, TDDS represent a valuable tool in modern pharmacotherapy.

CONFLICT OF INTEREST

The Authors declare that this article has no conflict of interest.

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